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Running Title: Ketamine-HCl in Lemmings

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Abstract

1. The effects of Ketamine-HCl anesthesia in the brown lemming (Lemmus trimucronatus) can be divided into four or five stages.
2. Females were more sensitive to this anesthetic than males. Females received 105 mg/kg, males, 120 mg/kg.
3. The drug appeared to be very satisfactory as an anesthetic base for lemmings during major operations, but only in combination with slight amounts of diethyl-ether (M's 120mg/kg; F's 105mg/kg).
4. It could be administered several times to the same animal at intervals of one day. The time required to arrive at a surgical plane of anesthesia played an important prognostical role.
5. Effects of the anesthetic, resuscitation when necessary, and post-surgical animal care are described.

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Introduction.

Environmental scientists have searched for an animal model for the northern regions to replace the temperate zone domestic white rat. The brown lemming is now being used for this purpose, since standardized inbred strains can be maintained in an Arctic environment.

We tried different injectable anesthetics, such as pentobarbital, chloralose, urethan, and Innovar on the brown lemming (Lemmus trimucronatus), but no safe dosage was found. In our laboratory ether alone has been successfully used with many species of animals, but with lemmings it was difficult to use and unsafe. When we found it necessary to do lemming pinealectomies, it was decided to look for another drug which would keep lemmings in an appropriate surgical plane for approximately 30 minutes. A preliminary test was done with Ketamine-HCl [a] using a non-standardized group (non-homogeneous) of 22 lemmings. The results of this test encouraged us to do a second and well-controlled study.

Materials and methods.

Ketamine-HCl was tested. In the preliminary non-standardized test, both wild-caught and laboratory-raised lemmings were used. The laboratory animals were bred and raised at the Naval Arctic Research Laboratory, Barrow, Alaska, which is situated at 71°18' N and 156°47' W. The wild-caught were all

[a] Ketamine-HCl (Veterinary Products, Bristol Laboratories)

captured within three miles of this Laboratory; their diet was not controlled and they were not conditioned to the same physical environment as the Laboratory strain. Two of these field animals in the series were later found to be pregnant. No animals were of known age.

In the controlled study only laboratory-raised animals were used. They were all standardized, i.e. they were maintained at their thermal neutral temperature (18°C), were on a 24-hour light cycle and had a diet consisting of carrot, Purina rat chow and water. Later all in this group except two were successfully pinealectomized. In all of these operations, ether by cone supplemented the Ketamine-HCl base. Several animals in both the preliminary and control study were injected a total of two to four times.

The drug was diluted in buffered water containing 0.25% sodium citrate, 0.5% glycerin, and 0.25% phenol. Buffered diluent was used instead of 0.9% saline because water was the original solvent. The drug was administered I.P. with a 0.5 inch needle (26 gauge); injections were made halfway between diaphragm and pelvis, just lateral to the umbilicus. The only justification for intraperitoneal injections was the ease of administration, although Galla warns that overdosage from I.P. injection is not as readily reversed as it is with inhalational techniques (1).

The following test dosages were used in the preliminary experiment: 40, 80, 160, 240, and 320 mg/kg. Only two dosages

were used in the second test: 105 and 120 mg/kg.

Results.

The animals were studied after this I.P injection and five stages or conditions could be observed. All these stages have also been described for inhalant anesthetics (2),(3):

Stage 1. Period of voluntary movement as a reaction to excitement; at the end uncoordinated.

Stage 2. Period of delirium; lost consciousness but still reacting to pinches in the abdominal skin. Muscular tremors and spastic jerking movements.

Stage 3. Period of surgical anesthesia, favored and maintained by light whiffs of ether. Sometimes the animals exhibit peculiar movements. There is no excess salivation.

Overdose Stage, Stage 4. In occasional cases, the medullary centers are blocked. Respiration ceases, but revival of the animal is possible with adequate resuscitation. Some of these lemmings die with symptoms of respiratory or cardiac failure or occasionally with a few convulsions with opisthotonus.

Recovery Stage, Stage 5. For most animals recovery follows spontaneously after Stage 3; they show hyperactivity by rapid circular running in the cage. This lasts sometimes for several hours.

The dose of 160 mg/kg was considered unsatisfactory (Table 1), since 6 out of 13 animals died. However, the

results indicated that a controlled study should be done. This controlled test was begun with a dose of 120 mg/kg (Table 2). Together with light ether during surgery, this was a successful choice; 91% of the males used entered Stage 3; pinealectomy could be done and excellent recovery followed (Table 2).

However, the dose was too high for females although some could be resuscitated. For most females a dose of 105 mg/kg was used, combined with ether; this new dose was successful with 9 out of 10 females. The 10th female was apparently more sensitive to Ketamine-HCl and quickly reached Stage 4. She was resuscitated and pinealectomy was done the next day, with a reduced dosage of 80 mg/kg (Table 2). Resuscitation was done by short, quick taps on the sides of the ribcage. The airway had to be opened and the tongue was pulled out.

During the recovery stage, all animals became hyperactive. Prognostically important seems to be the time required for the animal to arrive at Stage 3. Considering the dosages 80, 105, 120, and 160 mg/kg, it was found that the animals that died reached Stage 3 in 80 -15 secs. (±S.E.; N = 9), whereas those that recovered reached this stage in 218 -16 seconds (±S.E.; N = 27).

Discussion.

Whenever a new anesthetic is tried on a certain species, one should consider genetical differences, circadian rhythm,

nutritional status, individual variations and adaptation to the physical environment.

A characteristic of Ketamine-HCl was the variability of reactions on the same dosage; e.g. for 80 mg/kg, lemmings progressed to Stages 1, 2 or 3. In this varying degree of tolerance the strain within the species will play an important role (4). Besides that, some studies on the rat gave evidence that various drugs show big differences in rate of metabolism (5) (6) (7) which might explain why we could inject Ketamine-HCl several times into the same animal. This drug must be rapidly metabolized. However, only very few statements have been made about the influence of this drug on intermediary metabolism (8).

The time of day will influence responses to drugs; for example Davis describes the influence of circadian rhythms in the LD_{50} of pentobarbital in the mouse (9). For this reason we were careful to inject these animals only in the morning (9 AM to 11 AM).

Males and females respond differently to barbiturates in some species of rodents (10); therefore it is not surprising that our female lemmings need a dose 12.5% lower than males. However, this difference is contrary to findings of barbiturate effects in mice (11) (12) (13).

The nutritional status influences tolerance. Essential fatty acid deficient rats have a significantly higher sensitivity to diethylether (14). Nutrition was not well controlled in our experiment; this may explain why some moderate drug

injections were fatal. However, differences in age are known to add to the variations in responses (4). In both of our experiments the ages were unknown and part of the variable responses may be due to this factor.

Finally, animals should be adapted to the physical environment, i.e. cage, light cycle, and temperature; a well-adapted animal is more tolerant (15). In the preliminary test the animals were of mixed origin; some were laboratory-raised, but most were brought in from the field and immediately used. The animals used for the second study were laboratory-raised and had lived for at least two weeks in our test conditions; results with them were more consistent.

The LD_{50} in this experiment seems to be 160 mg/kg, since 6 out of 13 animals with this dose died.

One of the possible adverse reactions of Ketamine-HCl is cardiac arrest. Slight doses of ether might counteract this block, as an increase in blood catecholamines has been reported during ether anesthesia (16). Prognostically it is a bad sign if the animal goes down fast, possibly because it is significantly more sensitive.

After the operation, before recovery begins, the animal is hyperactive and should be protected against wounding itself on sharp edges of the cage. We used a cloth suspended like a basket in a box as a recovery enclosure. After one to four hours, the first food was consumed. especially if it was in wet form, such as apple. Within 24 hours the animals could tolerate their normal diet.

In summary, after trying numerous injectable anesthetics, we found Ketamine-HCl to be safe for surgery on an Arctic rodent species, the brown lemming; however, the drug had to be combined with light amounts of ether to sustain a surgical level.

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Table 1. Reactions to various doses of Ketamine-HCl Anesthetic in a preliminary study of lemmings of mixed origin.

Dosage mg/kg	No. of Animals	Stage Achieved 1	2	3	4
40	2	2	-	-	-
80	5	3	1	1	-
160	13	-	1	6	6 (died)
240	1	-	-	-	1 (died)
320	1	-	-	-	1 (died)
Total	22				

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Table 2. Reactions of male and female lemmings in a controlled study on Ketamine-HCl.

Dosage mg/kg	Sex	No. of Animals	Stage Achieved 1	2	3	4	
105	male	1	-	-	1*	-	
	female	10	-	-	9	1	(resuscitated)
120	male	11	-	-	10	1	(died)
	female	1	-	-	-	1	(died)

*Extra ether required.

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